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The Hofmann Rearrangement. IV. Kinetic Isotope Effect of *N*-Chlorobenzamide

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Kinetic isotope effects in the Hofmann rearrangement of phenyl-1-^{14}C and carbonyl-^{14}C labeled *N*-chlorobenzamides were measured in a sodium hydroxide solution at 15°C. The observed isotope effect on the phenyl-1-carbon is

$$k_{12}/k_{14} = 1.0456 \pm 0.0012$$

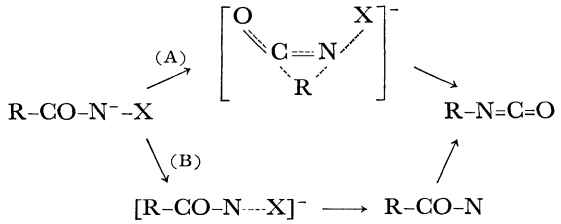
and that on the carbonyl-carbon is

$$k_{12}/k_{14} = 1.0447 \pm 0.0006$$

These results strongly support a concerted mechanism for this rearrangement. Attempts have been made to correlate the isotope effect on phenyl-1-carbon to the *r*-value of the linear aromatic substituent-reactivity relationship in related 1,2-rearrangements.

The most important stage in the course of the Hofmann reaction is the rearrangement step in which the conjugate base of *N*-haloamide is converted into isocyanate accompanying the release of a halide ion. With a view to clarifying the precise reaction mechanism of this step, we have investigated this rearrangement kinetically. Kinetic results of the rearrangements of various substituted *N*-bromo- and *N*-chlorobenzamides in an aqueous sodium hydroxide solution have been reported.[1-3] These results could be interpreted by considering a concerted mechanism (path (A)) rather than an alternative two-step mechanism (path (B)).

We have now studied the kinetic isotope effect of this rearrangement using phenyl-1-^{14}C and carbonyl-^{14}C labeled *N*-chlorobenzamides in order to demonstrate this concerted mechanism.



Results and Discussion

The rate of rearrangement of the non-labeled *N*-chlorobenzamide was measured at 15.00±0.01°C by the iodometric method. The initial concentrations of *N*-chloroamide and sodium hydroxide were 0.05 mol/*l*

1) T. Imamoto, Y. Tsuno, and Y. Yukawa, This Bulletin, **44**, 1632 (1971).
2) T. Imamoto, Y. Tsuno, and Y. Yukawa, *ibid.*, **44**, 1639 (1971).
3) T. Imamoto, Y. Tsuno, and Y. Yukawa, *ibid.*, **44**, 1644 (1971).

and 0.5 N, respectively.[4] The first-order kinetic plots formed straight line to at least 85% completion of the reaction. The rate constant obtained from repeated runs was $k_1=7.830\pm0.009\times10^{-5}$ sec^{-1}. This value is larger by *ca.* 1% than the one reported previously.[2] The slight difference in the rate constant refers to the change of the initial concentration of *N*-chloroamide from 0.025 to 0.05 mol/*l*.

Determination of the kinetic isotope effect was carried out under the same reaction conditions by measuring the specific activities of the benzamide derived quantitatively from the remaining reactant *N*-chlorobenzamide. Labeled *N*-chlorobenzamide, prepared from commercial benzoic-^{14}C acid, was dissolved in an aqueous sodium hydroxide solution. A certain amount of the reaction solution was pipetted out at intervals and transferred into hydrochloric acid containing excess potassium iodide. After reduction of the liberated iodine with a sodium thiosulfate solution, the benzamide was extracted and purified by recrystallization. The specific activity of the benzamide thus obtained was determined by an equilibrium voltage method with an ionization chamber and a vibrating reed electrometer connected to a digital integrating voltmeter. These results are listed in Table 2. The kinetic isotope effect was calculated by the least-squares method according to the equation

$$\log A_x = \log A_0 - (1-k_{14}/k_{12}) \log (1-x) \qquad (1)$$

where x is the fraction of reaction calculated from the reaction time and the rate constant ($k_1=7.830\times10^{-5}$ sec^{-1}), and A_x and A_0 are specific activities at $x=x$ and $x=0$ respectively. Figure 1 shows the plots of log A_x *vs.* log$(1-x)$. The calculated kinetic isotope effect on the phenyl-1-carbon is given by

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and that on the carbonyl-carbon by

$$k_{12}/k_{14} = 1.0447 \pm 0.0006$$

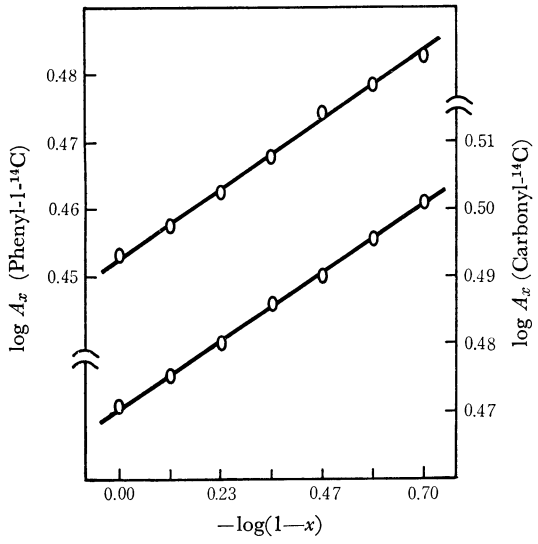
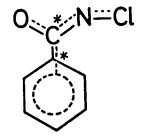


Fig. 1. Plots of log A_x *vs.* −log$(1-x)$

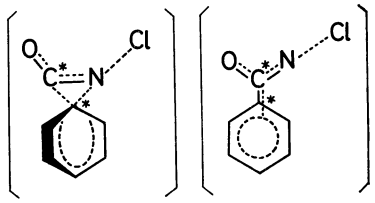
4) From the results of the preliminary experiment on the recovery and the purification of the residual unrearranged benzamide, 0.05 mol/*l* was employed as the most suitable initial concentration of *N*-chloroamide.

Theoretical and experimental studies on the isotope effect lead to the conclusion that the variation of bonding at a labeled position from the initial state to the transition state in the rate-determining step is the most important factor to cause a kinetic isotope effect.[5,6] Thus it is necessary, for elucidation of the precise reaction mechanism of the present Hofmann rearrangement, to examine the variations of the total bondings at respective labeled positions in *N*-chlorobenzamide for the proposed mechanisms.

The initial and transition states for the concerted and two-step mechanisms may be schematically represented as follows.



I. S.



T. S., Concerted T. S., Two-step

In the former mechanism, bondings at the labeled positions change remarkably in proceeding from initial to transition states, and measurable kinetic isotope effects can be expected in this mechanism. On the contrary, if the reaction proceeds through the two-step mechanism, no apparent kinetic isotope effect should be observed, since the transition state resembles the initial state with respect to the bondings at the labeled positions.

Thus the apparent kinetic isotope effects on phenyl-1- and carbonyl-carbons evidently indicate the concerted mechanism for the Hofmann rearrangement.[7]

In addition to the present Hofmann rearrangement, the kinetic isotope effects of Beckmann, Wolff and Schmidt rearrangements have been studied in our laboratory by the use of phenyl-1-^{14}C and carbonyl-^{14}C labeled compounds. The obtained results are summarized in Table 1. An important working hypothesis in the course of these studies is that the apparent observation of the kinetic isotope effect on phenyl-1-carbon indicates the participation of the phenyl group in electron-deficient migration terminus in the transition state. This suggests that the Hofmann and the Beckmann rearrangements proceed through a concerted type transition state. In the cases of other Wolff and Schmidt rearrangements, where kinetic isotope effects

5) J. Bigeleisen and M. Wolfsberg, *Advan. Chem. Phys.*, **1**, 15 (1958).

6) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press Co., New York, N. Y. (1960).

7) Wright and Fry studied the kinetic isotope effect of the Hofmann rearrangement using phenyl-1-^{14}C and carbonyl-^{14}C labeled *N*-bromobenzamides, and also supported the concerted mechanism. A. Fry, private communication.

TABLE 1. KINETIC ISOTOPE EFFECTS AND r-VALUES OF 1,2-REARRANGEMENTS

	Temp. (°C)	Phenyl-1-C k_{12}/k_{14}	Carbonyl-C k_{12}/k_{14}	r-Value
Hofmann rearrangement	15.00±0.01	1.0456±0.0012[a]	1.0447±0.0006[a]	0.41[g] (0.69)[h]
Beckmann rearrangement	60.00±0.01	1.018 ±0.009[b]		
	60.00±0.01	1.025 ±0.008[b]		0.632[i]
	40.00±0.01	1.026 ±0.003[b]		0.600[j]
	71.30±0.01	1.052 ±0.017[c]	1.00 ±0.01[c]	
Wolff rearrangement	30.00±0.01	1.00 ±0.01[d]	1.00 ±0.01[d]	−1.7[k]
Schmidt rearrangement	45.00±0.01	1.00 ±0.02[e]	1.045 ±0.02[e]	
	45.00±0.01		1.066 ±0.022[f]	

a) Present results.
b) Acetophenone oxime, in concd. H_2SO_4. Y. Yukawa, S. G. Kim, T. Ando, and T. Kawakami, unpublished.
c) Acetophenone oxime-acetate, in Beckmann mixture. Y. Yukawa and S. G. Kim, unpublished.
d) α-Diazoacetophenone, in t-butyl alcohol containing silver benzoate and triethylamine. Y. Yukawa and T. Ibata, This Bulletin, **42**, 802 (1969).
e) Acetophenone, in aqueous trichloroacetic acid containing sodium azide. Y. Yukawa and K. Toriyama, unpublished.
f) Benzophenone, in aqueous trichloroacetic acid containing sodium azide. Y. Yukawa and K. Toriyama, unpublished.
g) N-Chlorobenzamides, in 0.5 N NaOH, at 30°C. Ref. 2.
h) 2-Chloro 4- and 5-substituted N-chlorobenzamides, in 0.5 N NaOH, 30°C. Ref. 3.
i) Acetophenone oximes, in sulfuric acid, 51°C. P. J. McNulty and D. E. Pearson, *J. Amer. Chem. Soc.*, **81**, 612 (1959).
j) Acetophenone oxime-picrates, in dichlorobutane, 70°C. R. Huisgen, J. Witte, H. Walz, and W. Jira, *Ann. Chem.*, **604**, 191 (1957).
k) α-Diazoacetophenones, in toluene containing silver benzoate and triethylamine. Y. Yukawa, Y. Tsuno, and T. Ibata, This Bulletin, **40**, 2618 (1967).

on the phenyl-1-carbon were not observed within experimental error, the migration of the phenyl group might not take place in the rate-determining step.

On the other hand, application of the following LArSR relationship (linear aromatic substituent–reactivity relationship) is useful for elucidating the mechanisms of organic reactions.

$$\log k/k_0 = \rho(\sigma^0 + r\Delta\bar{\sigma}_R^+) \qquad (2)$$

In particular, empirical facts on the resonance parameter r have enabled us to evaluate quantitatively the degree of conjugation effect on the reactivity.[8]

The calculated r-values of Hofmann, Beckmann and Wolff rearrangements are given in Table 1. Comparatively large positive r-values of the former two rearrangements indicate the additional conjugation effect to the reaction center with the stabilization of the transition state. In contrast, the large negative r-value of the Wolff rearrangement shows that the resonance stabilization of the initial state is the most important factor in the reactivity.

It is of interest to compare these r-values with the kinetic isotope effects on phenyl-1-carbons. The positive r-value indicates an apparent isotope effect and the large negative r-value no effect. This leads to the conclusion that not only the application of the LArSR relationship but also the isotope effect study on phenyl-1-carbon are useful for the elucidation of the precise reaction mechanism of 1,2-rearrangement.

Experimental

Materials. N-*Chlorobenzamide-(Phenyl-1-*^{14}*C)*: A mixture of 10.0 g of phenyl-1-^{14}C labeled benzoic acid (supplied from NENC, USA) and 27 g of purified thionyl chloride was refluxed for 2 hr. The excess thionyl chloride was removed by azeotropic distillation adding twice 10 m*l* of absolute benzene. The benzoyl chloride obtained was added dropwise to 70 m*l* of 28% aqueous ammonia with stirring at 0—5°C. The benzamide precipitated was collected, washed with water and dried, mp 126.5—127.5°C, yield 8.11 g (82%). This crude amide was recrystallized three times from dichloroethane - ligroin (1:1), 6.60 g, mp 127.5—128.5°C. Specific activity 2.830 mCi/mol. The obtained pure amide (6.37 g) was dissolved in 400 m*l* of 3N HCl and chlorine gas was passed for 2 hr. The N-chloro derivative thus precipitated was collected, washed with water and dried *in vacuo*, 6.91 g (84%), mp 114—116°C. This was recrystallized twice from dichloroethane - ligroin (1:2), 5.38 g, mp 117.0—118.0°C (reported 117.0—118.0°C[2]). Active chlorine: found 22.85%, calcd. 22.79%. Specific activity 2.830 mCi/mol.

N-*Chlorobenzamide-(Carbonyl-*^{14}*C)*: Carbonyl-^{14}C labeled benzoic acid (supplied from RCC, England) (10.0 g) was converted into N-chlorobenzamide (4.95 g) by the same procedure as described in the preceding part. Benzamide: mp 127.5—128.5°C, specific activity 2.961 mCi/mol. N-chlorobenzamide: mp 117.0—118.0°C, specific activity 2.960 mCi/mol, active chlorine; found 22.73%, calcd 22.79%.

No mutual contamination of the phenyl-1-^{14}C and the carbonyl-^{14}C labeled N-chlorobenzamides was indicated by comparing the specific activities of the derived acetanilides with those of the respective reactants N-chlorobenzamides-^{14}C.

Determination of the Rate Constant. The rate constant of the rearrangement of non-labeled N-chlorobenzamide was determined at 15.00±0.01°C by the same procedure described previously.[1,2]

Measurement of the Kinetic Isotope Effect. Kinetic Procedure and Preparation of the Sample for Assay. In a measuring flask was placed 400 m*l* of a standardized aqueous sodium hydroxide solution (0.500N), and the flask was immersed in a constant temperature bath (15.00±0.01°C). Labeled N-chlorobenzamide (3.112 g) was weighed into a 500 m*l* Erlenmeyer flask and immersed in the same bath. After being kept for several hr, the sodium hydroxide solution was transferred into the Erlenmeyer flask with vigorous swirling. A certain amount of the reaction solution was pipetted out at intervals

8) Y. Yukawa, Y. Tsuno, and M. Sawada, This Bulletin, **39**, 2274 (1966); Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 783 (1965).

and transferred into 15 m*l* of 6N HCl containing 700 mg of potassium iodide. A sodium thiosulfate solution (0.3N) was added dropwise until the color of the liberated iodine disappeared. The residual unrearranged benzamide was extracted with five 50 m*l* portions of dichloromethane. The solvent was evaporated and the residue was stirred with 50 m*l* of dichloroethane. A small amount of the undissolved salts was excluded by filtration. The filtrate was evaporated to give pale yellow needles, *ca.* 120 mg, mp 125—127°C. This was recrystallized five times from toluene to afford 40—50 mg of sample for assay, colorless plates, mp 127.5—128.5°C.

Measurements of Specific Activity. About 7—8 mg of accurately weighed benzamide-^{14}C was burned by means of a combustion furnace for micro-elemental analysis, and the carbon dioxide generated was introduced into a 200 m*l* ionization chamber. The chamber was set on a Takeda-Riken RS-84 vibrating reed electrometer connected to a digital integrating voltmeter. The ion current was recorded as relative voltage every ten seconds for 1 hr, and the mean value of the voltage was obtained with the standard deviation of $\pm 0.2\%$. The radioactivity of the sample was calculated by calibration of the obtained voltage with that of the standard chamber. Specific activity measurements were carried out at least twice for each sample. Reproducibility of the specific radioassay was within 0.25% in every case. The results are given in Table 2. The error indicates the standard deviation from the mean value.

Table 2. Specific activities of residual unrearranged benzamide

No.	Time (min)	Fraction of reaction (%)	Specific activity (mCi/mol) Phenyl-1-^{14}C	Carbonyl-^{14}C
1	0	0	2.8404±0.0024[a)]	2.9567±0.0016[a)]
2	57.1	23.5	2.8666±0.0014	2.9877±0.0024
3	114.2	41.5	2.9011±0.0022	3.0257±0.0033
4	171.3	55.3	2.9357±0.0024	3.0629±0.0020
5	228.4	65.8	2.9805±0.0010	3.0914±0.0016
6	285.5	73.9	3.0101±0.0011	3.1287±0.0004
7	342.6	80.0	3.0389±0.0029	3.1690±0.0040

a) The sample was obtained by treatment of pure *N*-chlorobenzamide with potassium iodide in aqueous acetic acid.

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